

Exhibit 34

The Rising Cost of Insulin

Why the price of this lifesaving drug is reaching new heights

By Allison Tsai
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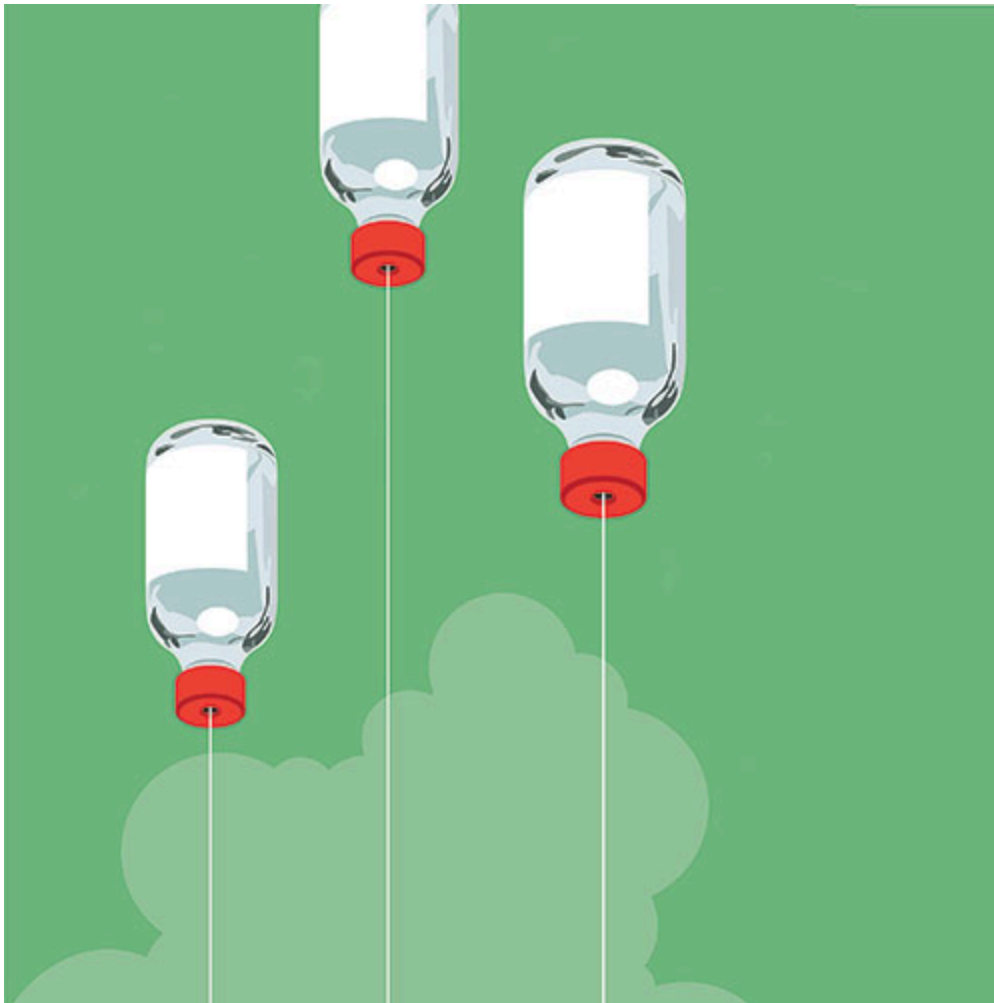


Illustration by Steve McCracken

Two men and \$3 changed the course of diabetes treatment. In 1921, Canadian scientists Frederick Banting and Charles Best discovered insulin—a development that altered the outlook for people living with diabetes. Because this discovery could save lives, Banting, Best, and James Collip, their colleague who purified the insulin, sold the patent to the University of Toronto for \$1 Canadian each, with the hope that affordable insulin would become available quickly.

The scientists made it clear that their motivation was for the good of humanity rather than commercial profit. But in order to keep up with demand and produce insulin on a large scale, the University of Toronto

signed nonexclusive licenses with medical companies such as Eli Lilly, which went on to produce enough insulin for all of North America by 1923—a move that opened the doorway to the privatization and commercialization of insulin.

In 2014, almost 93 years after the scientists' gesture of goodwill, insulin was a \$24 billion global industry—and it's expanding fast. According to a report from P&S Market Research, by 2020 the global insulin market will top \$48 billion.

Unfortunately, the cost to consumers is also rising, particularly for those who are uninsured or underinsured and those who need large total daily doses. While it's easy to point blame at pharmaceutical companies for increasing prices, certain information about manufacturing costs and health insurance plan discounts is confidential, which makes it difficult to say how prescription drugs are priced.

And drug company profits aren't a bad thing. A portion of that money goes back into research and development to innovate and create better insulin products for the future. But the question remains: What good are these new products if the people who need them can't afford them?

The Prescription Drug Game

The cost of a vial of insulin starts with the pharmaceutical company and how it sets a price for insulin or any other drug. Algorithms and formulas, along with basic business decisions, inform this price. "Much of how we set price is based on the clinical benefit combined with our—and payers'—understanding about how diabetes can be effectively managed to reduce long-term complications and additional costs those complications place on the health care system," says Ken Inchausti, a spokesman for Novo Nordisk.

But remember, this is a for-profit industry: Companies might increase the price, for instance, if sales are lower than expected, a competitor will be coming on the market soon, or the patent on a drug is expiring. Or, they may price to match or undercut a competitor to win more market share.

The pharmaceutical company's set price, called the average wholesale price, is not the price that anyone will theoretically pay, says Irl Hirsch, MD, professor of medicine in the Division of Metabolism, Endocrinology, and Nutrition at the University of Washington. "It's similar to when you buy a car," he says. "You go see a car [that] costs \$30,000, but everybody, including the dealer and the person looking at the car, knows that nobody is going to pay that much money—there [are] going to be negotiations."

Eli Lilly spokesman Greg Kueterman agrees. "Importantly, the list price—typically the center of the price discussion—is not what manufacturers receive," he says. "Rather, it is a starting point for negotiations." Negotiations are confidential and occur between the pharmaceutical companies and middlemen. The results influence how much someone will pay at the pharmacy.

According to Avalere, a business and health care policy analyst firm, these middlemen include drug wholesalers and distributors, pharmacy benefit managers, health plans, and sometimes large retail pharmacy chains, which all negotiate price discounts, often pitting competing pharmaceutical companies against one another to get lower prices. During this process, the middlemen also take a cut of the profit from the negotiations, so they may mark up the drug or may not pass along deep price cuts to their customers.

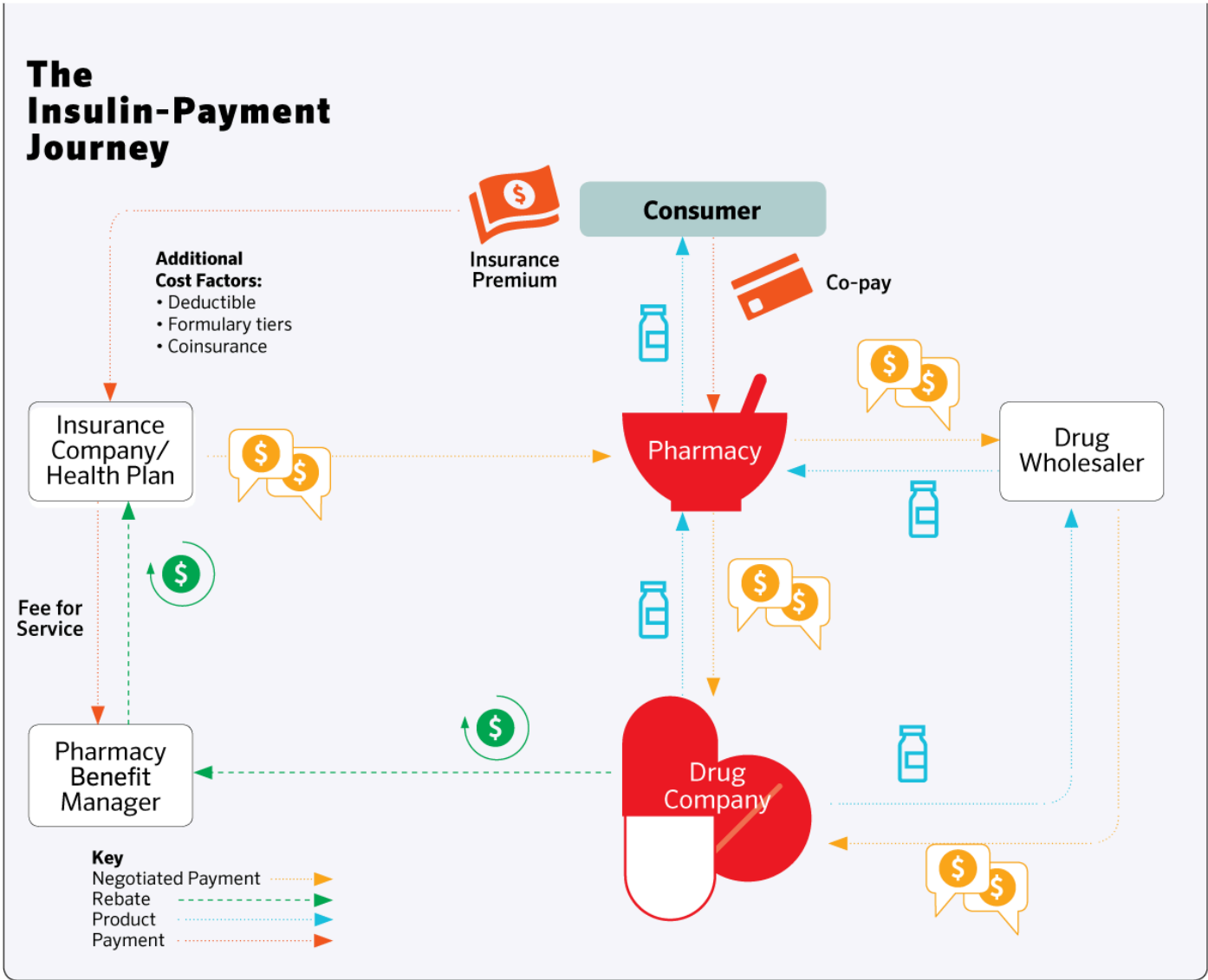
Pharmacy benefit managers often work on behalf of commercial and government-run health plans to negotiate drug prices, though there are regulations for Medicaid and Veterans Administration plans to ensure that prices can't rise above a certain level. Pharmacy benefit managers conduct comparative drug research and develop formularies—tiered lists of prescription drugs covered by a health plan. This is where pharmacy benefit managers have quite a bit of negotiating power. If they've determined that several insulin products have the same efficacy and side effect profile, then they look at the cost to the

plan. Insulin that costs the plan the least will land on a lower tier on the formulary—and have a cheaper copay.

Copay is key with drug manufacturers, who know patients are more likely to buy drugs that cost them less. So they'll offer pharmacy benefit managers big discounts to make their drug more attractive. They may offer an additional discount to better position their drug against competitors—so their drug ends up on a lower tier while their competitor's is on a higher tier with higher copays.

Cash and Rebate Flow

To make matters more confusing, discounts are not given up front. For instance, if you pay a \$35 copay at the pharmacy, the pharmacy will bill your health plan to recoup the rest of the cost. All of these negotiations are confidential, so we don't know the discounts and prices agreed upon within this process. See the flow of insulin, payments, and rebates among the parties involved, below.



Click the image to enlarge.

In the Shadows

When it comes to insulin, some brands, including Humulin R, Levemir, and Lantus, have increased in wholesale price by more than 160 percent in the past five years, according to a 2015 Bloomberg Health

report. It started with a price hike for Lantus, followed by a similar increase for Levemir, and so on—a practice called shadow pricing.

While this increase is alarming, it's less so for people with insurance: With the negotiated discounts and rebates, the wholesale price isn't the cost an insured person will pay. (For instance, the price Lilly received for Humalog after all negotiations rose by only 4 percent between 2009 and 2014, Kueterman says.) But depending on your plan, these increases may still have an effect. "Over the last few years, many people have moved from traditional copay insurance plans, where they paid predictable copay prices for prescription medicine, to high-deductible or coinsurance plans, leading to higher and unpredictable list prices for extended periods of time, says Kueterman. In the Affordable Care Act's state health insurance marketplace, Hirsch says, many people purchase plans with high deductibles—up to \$6,000—that don't cover drugs. While they pay a low premium every month, they'll have to pay the full price on insulin until they reach that \$6,000 benchmark to receive medicine benefit coverage from the plan. In some plans, medication is not subject to a deductible, so do your research before you buy.

It's also possible that copays or coinsurance percentages are rising to meet the increased cost of these drugs. Endocrinologist Kasia Lipska, MD, MSH, assistant professor of medicine at the Yale School of Medicine, has numbers to back that up. In her 2014 *Journal of the American Medical Association* study on the use and out-of-pocket costs of insulin for people with type 2 diabetes, she found that among the commercially insured population that her team analyzed, out-of-pocket costs for insulin increased by 89 percent from 2000 to 2010.

"I see a lot of patients in my clinical practice who cannot afford the insulin they are taking," she says. "I have to work with them and discuss the financial implications of using one versus the other, because it really matters. Sometimes it's between taking the insulin and paying their bills."

Analog Versus Human

Lipska was surprised by some of her findings: "Human insulin has become almost entirely obsolete in private clinical practice," she says. That's partially because analogs—such as NovoLog, Humalog, and Lantus—are made to more closely mimic how the body secretes insulin. "They can be used in more flexible ways," Lipska says.

Because of faster action, rapid-acting analogs can be dosed close to the start of meals instead of 30 minutes before.

But, in terms of evidence, Lipska says the benefits of analogs for people on basic insulin therapy are not as clear-cut. "We know that, in people with **type 2**, the long-acting insulin analogs may be associated with a little bit less **hypoglycemia** at night, but otherwise, when you compare head-to-head in terms of analog versus human insulin, there aren't big differences in terms of glycemic [blood glucose] control or the safety of these different preparations," she says. In addition, Hirsch says the long-acting analogs have not shown improvements in hypoglycemia for people with type 2 the way they have for people with **type 1**.

Once you weigh that evidence, consider cost. Insulin analogs are often seven to eight times more expensive than human insulins, says Lipska. That's especially costly for people who take large doses of analog insulin daily.

The short-term solution: If you're on basic insulin therapy, discuss with your doctor the possibility of switching to less expensive human insulin.

Cost drove Geralyn McGrath, 53, of Tucson, Arizona, to switch from Lantus, an analog, to Humulin 70/30, a mix of two types of human insulin. Lantus cost her \$190 with insurance. McGrath, who was diagnosed with type 2 a year ago, kept up with the costs for about six months before asking her doctor to switch her

to human insulin. "I told my doctor, 'I just can't do it anymore. It's just strapping us,'" she says. "I couldn't have anything extra in my life."

Now she pays \$126 for her insulin. It's better, but the cost still puts a strain on her family's finances. "We manage to survive, but we shouldn't have to pay so much for something we need to live," she says.

The good news? McGrath says her blood glucose control is about the same on human insulin as it was on analog. The only downside is convenience. "I liked that I had to [take Lantus] once a day," rather than at mealtimes throughout the day, she says.

You should know: If you decide to pay \$25 out of pocket for human insulin at Walmart rather than go through your insurance, you may run into problems, especially if you have type 1. Your insurance may believe you're not on insulin anymore because you're not getting it through them. "So now the insurance won't pay for strips, won't pay for continuous glucose monitors, [and] won't pay for pump supplies," Hirsch says. The solution: Ask your pharmacist to run the insulin through the online billing system for the insurer with a \$0 charge so your supplies are still covered.

Skyrocketing Prices

Government programs typically get some of the lowest-available prices for prescription medications—but they've been paying more for insulin, too. In a 2015 JAMA Internal Medicine article on trends in Medicaid reimbursements for insulin, Jing Luo, MD, a research fellow in the Division of Pharmacoepidemiology and Pharmacoeconomics at Boston's Brigham and Women's Hospital, found that no matter how he cut up the data, insulin of all types was increasing in price.

Luo and his team discovered that between 1991 and 2014, the amount of money Medicaid paid pharmacies per unit of insulin increased by between \$6.86 and \$15.38, depending on insulin type. And they found that the rate of increase was higher for insulin with patent protection. (What the study didn't determine, though, was whether the rebates pharmaceutical companies send Medicaid offset the price hikes.)

Overall, Luo says these increasing prices likely have an effect on government-run programs such as Medicaid and Medicare Part D and, in turn, the people who use their services. For instance, programs may try to contain costs by implementing prior authorization for medications, which means your plan will review your situation and requested medications before it agrees to cover the drug.

The Donut Hole

Drug cost is a major issue for people using Medicare prescription drug coverage, which is available only through private insurers. In most plans, there is a coverage gap, also known as "the donut hole." Once you've spent a certain amount of money on covered drugs, plus your deductible, you enter the donut hole, where you pay a larger percentage of the price of each drug until you spend another benchmark amount of money and get out of the donut hole. When you're in the donut hole, the price of the drug really matters because you pay a percentage of that to fill your prescription.

In 2016, once you and your plan have spent \$3,310 on covered drugs, you're in the donut hole. At this point, you will be responsible for 45 percent of the price of brand-name drugs and 58 percent of the price of generic drugs.

So how do you get out of the donut hole? Spend money on brand-name prescriptions. For those, your 45 percent and the 50 percent manufacturer discount both apply toward reaching that next benchmark. For generic drugs, only what you pay applies. Once you hit \$4,850 in 2016, you will be out of the donut hole.

At that point, you'll have what's called catastrophic coverage, and you have to pay only a small coinsurance or copay for covered drugs for the rest of the year.

Good news: The donut hole will be closing in 2020, at which time people on Medicare will pay one price throughout the year.

Brace for Impact

"Type 2 diabetes is a condition that impacts minorities and lower socioeconomic people more," says Hirsch. And they're the ones who are suffering the most with the rising costs. To make ends meet, some people are engaging in risky behaviors, such as rationing insulin. This can lead to sustained hyperglycemia and, in severe cases, diabetic ketoacidosis.

It's also common for people to skip refills on prescriptions they can't afford. "Some patients might not tell their doctor they're having difficulty paying for the medicine," Lipska says. "They might just not fill it, and that would be the worst outcome."

In the type 1 population, Hirsch says some people are stretching their insulin by severely limiting carb intake or just letting their blood glucose run high, which can lead to a host of complications. Pharmaceutical patient assistance programs, which offer discounts to qualifying consumers, can be useful in such situations.

Price issues show up in other ways, too, even for people with insurance. Hirsch says a patient of his forgot her insulin one day when she was an hour away from home. She went to the pharmacy to pick up another vial, and it cost her \$250: the full price of the insulin.

For people who have made the switch back to cheaper human insulin from more expensive analogs, there are still worries. "My biggest concern is that the companies are going to stop making [older insulin], because they don't feel that they can make as many millions—and, frankly, billions—of dollars," Hirsch says.

And there is a larger philosophical issue at play. We're up against an unsustainable cost increase, and at some point there will be sacrifices to care.

"We are literally going backwards," says Hirsch. "We are going back to using old insulins, we are seeing more ketoacidosis, everything that we were supposed to see moving forward with better pharmaceuticals, better innovation, in actuality, they've outpriced it."

Lack of Competition

The United States, unlike some other countries around the world, does not regulate the price of prescription drugs. One of the reasons insulin is rising in price so much is, essentially, because drug companies set the starting price—and lifesaving insulin must be purchased.

"We don't have a very healthy competitive insulin market," says Lipska. As it is, only a few companies make insulin, and the cost of all of them keeps going up. This suggests there's no real price competition.

Typically, the price of a prescription will be tempered when generic drugs enter the market after patents expire. These cheaper generics create competition for brand-name drugs, forcing them to bring down their prices.

So, where are these generic forms of insulin? Currently, there are no generic insulin products in the United States, and the reason why is complicated. For one, insulin is considered a biologic rather than small-

molecule drug because it's made from living cells, and all generic forms of biologics, called biosimilars, are subject to more stringent approval standards than small-molecule generics. So it's much more expensive, more complex, and more difficult to achieve a "copy" of the original.

Because of the larger financial burden of manufacturing biosimilars, they would likely not lead to the same 90 percent price reduction seen with other generic meds. Experts estimate that it would be more like a 20 to 40 percent reduction in price, says Lipska, though most are leaning toward the low end of that range. Still, that should bring down the price of some of the most costly insulin, particularly the analogs.

How soon until we see a biosimilar hit U.S. markets? Basaglar, a pen-based version of insulin glargine manufactured by Eli Lilly and Boehringer Ingelheim, is approved as a biosimilar in Europe and as a follow-on medication (a drug similar to an already approved product) in the United States. The launch date is currently December 2016.

The dawn of these biosimilars is one reason prices are out of control, says Hirsch: Drug companies are trying to rake in as much money as they can before these cheaper alternatives enter the market.

Long-Term Solutions

Aside from biosimilars entering the market to create healthy competition for brand-name insulin, action in other ways could help this growing problem.

One controversial solution is for the government to step in with some kind of regulation. "I wonder if putting a ceiling on how much insulin companies can charge for insulin would be one option," says Lipska.

Luo agrees that some kind of regulation could help, because what's happening now isn't working. "The way Congress has mandated it [for Medicare] is that we shall have the private market take care of drug prices," he says. But as Lipska's research shows, costs haven't been contained through the private market.

A more-promising solution, he says, is to start a dialogue with all of the big players, including insulin companies and pharmacy benefit managers. "We need to open dialogue with everybody so that people realize the massive profit-taking that has happened in the last few years can't happen with insulin the way it's happening with the rest of medicine."

This sentiment is gaining ground in the cost conversation, and serves as an important reminder. The humanitarian spirit accompanied the discovery of insulin, and its lifesaving ability remains. "It's not a concierge item," says Hirsch. "It's required for survival."

Pricing Solutions

According to the American Diabetes Association, insulin is a unique medication: When it is needed, there are no alternative therapies to preserve health and life. The Association supports high-quality diabetes therapies that are available and affordable for all people with diabetes, noting that people in need of lifesaving medication should never go without due to prohibitive costs or accessibility issues.

Numerous public policy and private sector solutions are emerging on how to make this a reality. The Association supports several promising avenues for change, including:

- Wanting to see all off-patent diabetes medications, including insulin, in the lowest cost-sharing tier on all formularies
- Supporting the authorization of the Centers for Medicare and Medicaid Services (CMS) to negotiate prices for prescription drugs under Medicare Part D

- Supporting the move toward value-based benefit design from the current fee-for-service system to incentivize better outcomes, in addition to promoting adherence to recommended therapy to reduce emergency department visits and hospitalizations.

Urging transparency in pricing policies by all parties involved in the numerous steps that it takes for medications to travel from the manufacturer to the consumer, the Association also strongly encourages continued dialogue across the diabetes marketplace, in public policy and in the private sector, to develop lasting, affordable solutions.

More Online

Head to diabetesforecast.org/insulinchart for a list of current insulins on the market, their characteristics, how they're delivered, and more

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